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Date: Oct. 30, 2003

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT	: SAMUEL ROSE, M.D. (Deceased June 3, 2001)
CPA OF SERIAL NO.	: 08/782,590, filed August 13, 2001
CPA FILED	: October 30, 2003
FOR	: A METHOD AND COMPOSITION FOR TREATING CANCER BY CONVERTING SOLUBLE RADIOACTIVE TOXIC AGENTS INTO INSOLUBLE RADIOACTIVE TOXIC PRECIPITATES VIA THE ACTION OF NON-MAMMALIAN ENZYMES BOUND TO THE NON-ENDOCYTOSING RECEPTORS OF TARGET CELLS
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PRELIMINARY AMENDMENT FOR CONTINUED PROSECUTION APPLICATION (CPA) UNDER 37 CFR. 1.53 (d)

SIR:

In view of the Official Action, mailed May 1, 2003, the following claims 1-83 are submitted for the above identified CPA Application:

1. A method for treating a heterogeneous population of cancer cells in a living host by at least one of a first therapeutic agent and an additional therapeutic agent, the living host being including normal cells growing in a normal extra-cellular matrix having at least collagen and fibronectin, the heterogeneous population of cancer cells growing in a cancer-altered extra-cellular matrix having at least cancer-altered antigenic epitopes, the heterogeneous population of cancer cells endogenously making and containing products including at least sulphated glycosaminoglycans, natural intra-cellular enzymes in the lysosomes, and natural intra-cellular material including DNA, histone, and complexes of DNA-histone, the DNA, histone, and complexes of DNA-histone having antigenic epitopes, the heterogeneous population of cancer cells including at least four sub-populations of cancer cells:

the first sub-population of cancer cells being first target cancer cells each having a first antigenic receptor which is substantially specific to a cancer cell and which is capable of binding a first targeting agent, the first antigenic receptor being incapable of endocytosis when the first targeting agent binds to the first antigenic receptor;

a second sub-population of cancer cells being the second target cancer cells each having a second antigenic receptor which is substantially specific to a cancer cell and which is incapable of endocytosis;

a third sub-population of cancer cells being the third target cancer cells each having a high sensitivity to being killed by the natural system of the living host and a high sensitivity to being killed by the natural system of the living host;

a fourth sub-population of cancer cells being non-target cancer cells which are the remainder of the heterogeneous population of the cancer cells; and

the normal cells of the living host in addition endogenously making and containing products including at least sulphated glycosaminoglycans, natural intra-cellular enzymes in the lysosomes, and natural intra-cellular material including DNA, histone, and complexes of DNA-

histone, the DNA, histone, and complexes of DNA-histone having antigenic epitopes, the normal cells including at least two sub-populations of normal cells:

the first sub-population of normal cells being the first target normal cells having the first antigenic receptor which is capable of binding the first targeting agent, the first antigenic receptor being incapable of endocytosis when the first targeting agent binds to the first antigenic receptor;

a second sub-population of normal cells being non-target normal cells which are the remainder of the normal cells;

the method comprising the steps of:

introducing into the living host a first bispecific reagent having two moieties, a first moiety which is a non-mammalian enzyme moiety being a first enzyme moiety, the first bispecific reagent further having a second moiety including a targeting agent moiety which has a substantial affinity for the first antigenic receptor of the first target cancer cells and the first target normal cells;

permitting the first bispecific reagent to bind to the first antigenic receptor of the first target cancer cells and of the first target normal cells, the first bispecific reagent being received and bound at the first antigenic receptor of the first target cancer cells and of the first target normal cells, the first bispecific reagent thereby being retained in the extra-cellular fluid for an extended period of time which enables the first enzyme moiety to convert a substantial amount of the first therapeutic agent in the extra-cellular fluid into an insoluble non-digestible precipitate which is a first extra-cellular precipitate, the first extra-cellular precipitate being capable of remaining in the extra-cellular fluid adjacent to the first bispecific reagent for an extended period of time;

administering to the living host the first therapeutic agent which is a soluble precipitable material and which is converted by the first enzyme moiety of the first bispecific reagent into the first extra-cellular precipitate, the first extra-cellular precipitate having at least one of a first antigenic epitope being an epitope which is an integral part of the structure of the first extra-cellular precipitate, a second antigenic epitope, and a neo-antigenic third epitope, the first extra-cellular precipitate forming in the extra-cellular fluid adjacent to the first bispecific reagent and being

capable of remaining in the extra-cellular fluid adjacent to the first bispecific reagent for an extended period of time;

continuing the introducing of the first therapeutic agent into the living host to increase the amount of the first extra-cellular precipitate forming in the extra-cellular fluid, the continued administration of the first therapeutic agent thereby causing an accumulation of first extra-cellular precipitate to form in the extra-cellular fluid, the accumulation of the first extra-cellular precipitate thereby having a plurality of antigenic epitopes which is proportional to the amount of accumulation;

additionally introducing to the living host a second bispecific reagent having two moieties, a first moiety being a non-mammalian enzyme moiety which is a second enzyme moiety including a targeting agent moiety having a substantial affinity for at least one of the first antigenic epitope, the second antigenic epitope, and the neo-antigenic third epitope of the first extra-cellular precipitate;

further permitting the second bispecific reagent to bind to at least one of the first antigenic epitope, the second antigenic epitope, and the neo-antigenic third epitope of the first extra-cellular precipitate, the second bispecific reagent being received and bound at the first extra-cellular precipitate which is retained in the extra-cellular fluid for an extended period of time, thereby enabling the second enzyme moiety to convert a substantial amount of an additional therapeutic agent into a new form capable of remaining in the extra-cellular fluid adjacent to the first extra-cellular precipitate for an extended period of time which is sufficient to kill non-selectively all cells adjacent to the first extra-cellular precipitate; and

additionally administering to the living host the additional therapeutic agent which is a soluble radioactive toxic agent to be converted by the second enzyme moiety into the new form capable of remaining in the extra-cellular fluid adjacent to the first extra-cellular precipitate for an extended period of time which is sufficient to kill non-selectively all cells adjacent to the first extra-cellular precipitate.

2. A method in accordance with claim 1 in which the first enzyme moiety is beta lactamase.

3. A method in accordance with claim 1 in which the first enzyme moiety is a penicillinase.

4. A method in accordance with claim 1 in which the first enzyme moiety is a glycosidase.

5. A method in accordance with claim 1 in which the first therapeutic agent is a soluble agent and is an organic chemical comprising at least one of peptides, including opio-melanins, of carbohydrates including cellulose, chitosan, and chitin, of proteoglycans, of synthetic polymers, and of indoxyl compounds having molecular positions 1-7.

6. A method in accordance with claim 1 in which the first therapeutic agent is inherently cell impermeant.

7. A method in accordance with claim 1 in which a cell-impermeant chemical is attached to the first therapeutic agent the cell-impermeant chemical causing the additional therapeutic agent to be cell impermeant.

8. A method in accordance with claim 7 in which the cell-impermeant chemical includes one of thiol, anionic materials, and materials having a molecular weight greater than 1000 daltons.

9. A method in accordance with claim 1 in which the first therapeutic agent is inherently a soluble molecule which is converted by the first enzyme moiety of the first bispecific reagent into a new form which is insoluble and forms the first extra-cellular precipitate.

10. A method in accordance with claim 1 in which the first therapeutic agent is inherently a soluble molecule which is converted by the first enzyme moiety of the first bispecific reagent into a new form which is insoluble and forms the first extra-cellular precipitate, the first extra-cellular precipitate having a neo-antigenic epitope not present on the first therapeutic agent from which the first extra-cellular precipitate was formed.

11. A method in accordance with claim 1 in which the first therapeutic agent is converted by the first enzyme moiety of the first bispecific reagent into a soluble intermediate molecule, the soluble intermediate molecule being naturally converted in the extra-cellular fluid into a molecule which is insoluble and forms the first extra-cellular precipitate.

12. A method in accordance with claim 1 in which the first therapeutic agent is rapidly oxidized, the oxidized soluble intermediate molecule spontaneously being dimerized and thereby making a new molecule which is insoluble and forms the first extra-cellular precipitate, the first extra-cellular precipitate having a neo-antigenic epitope <u>not</u> present on the first therapeutic agent from which it was formed.

13. A method in accordance with claim 5 in which the indoxyl compounds include at least one of indoxyl-penicillin, indoxyl-cephalosporin, indoxyl-glycosides and the like which when attached to position 3 of the indoxyl compounds are cleavable by the first enzyme moiety of the bispecific reagent, the material remaining after cleaving at position 3 being a soluble reactive intermediate molecule which oxidizes and dimerizes to make a new insoluble molecule which is insoluble and forms the first extra-cellular precipitate.

14. A method in accordance with claim 5 in which each of the indoxyl compounds includes a substance when attached to at least one of positions 4, 5, 6, and 7 of the indoxyl compound alters the characteristics of the indoxyl compounds and the first extra-cellular precipitate.

15. A method in accordance with claim 5 in which each of the indoxyl compounds includes phenyl compounds attached at position 5 of the indoxyl compound to alter the characteristics of the indoxyl compounds and the first extra-cellular precipitate.

16. A method in accordance with claim 5 in which each of the indoxyl compounds includes benzyloxy compounds and all the derivatives of benzyloxy attached at position 5 of the indoxyl compounds to alter the characteristics of the indoxyl compounds and of the first extra-cellular precipitate.

17. A method in accordance with claim 5 in which each of the indoxyl compounds includes 5,5-bi-indoxyls attached at position 5 of the indoxyl compounds to alter the characteristics of the indoxyl compounds and of the first extra-cellular precipitate.

18. A method in accordance with claim 1 in which the first therapeutic agent has a soluble moiety and an insoluble moiety, the soluble moiety having a solubilizing effect on the insoluble moiety and being cleaved by the first enzyme moiety of the first bispecific reagent from the insoluble moiety, the solubilizing effect of the soluble moiety being thereby dissipated and the remaining material, having been converted into a new form and being insoluble, spontaneously precipitates, and forms the first extra-cellular precipitate.

19. A method in accordance with claim 1 in which the second enzyme moiety is beta lactamase.

20. A method in accordance with claim 1 in which the second enzyme moiety is a penicillinase.

21. A method in accordance with claim 1 in which the second enzyme moiety is a glycosidase.

22. A method in accordance with claim 1 in which the second enzyme moiety is chondroitinase ABC.

23. A method in accordance with claim 1 in which the targeting agent moiety of the second bispecific reagent has a substantial affinity for the first antigenic epitope of the first extra-cellular precipitate.

24. A method in accordance with claim 1 in which the targeting agent moiety of the second bispecific reagent has a substantial affinity for the second antigenic epitope of the first extra-cellular precipitate.

25. A method in accordance to claim 1 in which the targeting agent moiety of the second bispecific reagent has a substantial affinity for the neo-antigenic third epitope of the first extra-cellular precipitate.

26. A method in accordance with claim 1 in which the additional therapeutic agent is a soluble radioactive toxic agent and is an organic chemical comprising at least one of peptides, including opio-melanins, of carbohydrates including cellulose, chitosan, and chitin, of proteoglycans, of synthetic polymers, and of indoxyl compounds having molecular positions 1-7.

27. A method in accordance with claim 1 in which the additional therapeutic agent is inherently cell impermeant.

28. A method in accordance with claim 1 in which a cell-impermeant chemical is attached to the additional therapeutic agent the cell-impermeant chemical causing the additional therapeutic agent to be cell impermeant.

29. A method in accordance with claim 28 in which the cell-impermeant chemical includes one of thiol, anionic materials, and materials having a molecular weight greater than 1000 daltons.

30. A method in accordance with claim 1 in which the additional therapeutic agent being the second therapeutic agent is inherently a soluble molecule which is converted by the second enzyme moiety of the second bispecific reagent into a new form which is insoluble and forms the second extra-cellular precipitate.

31. A method in accordance with claim 1 in which the additional therapeutic agent being the second therapeutic agent is inherently a soluble molecule which is converted by the second enzyme moiety of the second bispecific reagent into a new form which is insoluble and forms the second extra-cellular precipitate, the second extra-cellular precipitate having a neo-antigenic epitope not present on the second therapeutic agent from which the second extra-cellular precipitate was formed.

32. A method in accordance with claim 1 in which the additional therapeutic agent being the second therapeutic agent is converted by the second enzyme moiety of the second bispecific reagent into a soluble intermediate molecule, the soluble intermediate molecule being naturally converted in the extra-cellular fluid into a molecule which is insoluble and forms the second extra-cellular precipitate.

33. A method in accordance with claim 1 in which the additional therapeutic agent being the second therapeutic agent is rapidly oxidized, the oxidized soluble intermediate molecule spontaneously being dimerized and thereby making a new molecule which is insoluble and forms the second extra-cellular precipitate, the second extra-cellular precipitate having a neo-antigenic epitope not present on the second therapeutic agent from which it was formed.

34. A method in accordance with claim 26 in which the indoxyl compounds include at least one of indoxyl-penicillin, indoxyl-cephalosporin, indoxyl-glycosides and the like which when attached to position 3 of the indoxyl compounds are cleavable by the second enzyme moiety of the second bispecific reagent, the material remaining after cleaving at position 3 being a soluble reactive intermediate molecule which oxidizes and dimerizes to make a new insoluble molecule which is insoluble and forms the second extra-cellular precipitate.

35. A method in accordance with claim 26 in which each of the indoxyl compounds includes a substance when attached to at least one of positions 4, 5, 6, and 7 of the indoxyl compound alters the characteristics of the indoxyl compounds and the second extra-cellular precipitate.

36. A method in accordance with claim 26 in which each of the indoxyl compounds includes phenyl compounds attached at position 5 of the indoxyl compound to alter the characteristics of the indoxyl compounds and the second extra-cellular precipitate.

37. A method in accordance with claim 26 in which each of the indoxyl compounds includes benzyloxy compounds and all the derivatives of benzyloxy attached at position 5 of the indoxyl compounds to alter the characteristics of the indoxyl compounds and of the second extra-cellular precipitate.

38. A method in accordance with claim 26 in which each of the indoxyl compounds includes 5,5-bi-indoxyls attached at position 5 of the indoxyl compounds to alter the characteristics of the indoxyl compounds and of the second extra-cellular precipitate.

39. A method in accordance with claim 1 in which the additional therapeutic agent being the second therapeutic agent has a soluble moiety and an insoluble moiety, the soluble moiety having a solubilizing effect on the insoluble moiety and being cleaved by the second enzyme moiety of the second bispecific reagent from the insoluble moiety, the solubilizing effect of the soluble moiety being thereby dissipated and the remaining material, having been converted into a new form and being insoluble, spontaneously precipitates, and forms the second extra-cellular precipitate.

40. A method in accordance with claim 1 in which the additional therapeutic agent being the third therapeutic agent is converted by the second enzyme moiety of the second bispecific reagent into a new form, the new form being a soluble material having a neo-antigenic epitope not present on the third therapeutic agent from which the new form was created.

41. A method in accordance with claim 40 in which the third therapeutic agent is chondroitin sulphate which is converted by the second enzyme moiety of the second bispecific reagent into a new form, the new form of the third therapeutic agent being a soluble material with a neo-antigenic epitope not present on the chondroitin sulphate from which the new form of the third therapeutic agent was created.

42. The method in accordance with claim 40 and further comprising the step of administering to the living host a precipitating antibody having a specific affinity for the neo-antigenic epitope on the new form of the third therapeutic agent, the precipitating antibody being administered prior to the step of administering the third therapeutic agent and having the ability to bind to the neo-antigenic epitope of the new form of the third therapeutic agent, the binding causing the new form of the third therapeutic agent to form a third extra-cellular precipitate which remains for an extended period of time adjacent to the relocated first extra-cellular precipitate.

43. A method according to claim 1 and further comprising the step of administering to the living host a third bispecific reagent to tether the first extra-cellular precipitate, the third bispecific reagent having two moieties, the first moiety having an affinity for one of the first antigenic epitope, the second antigenic epitope, and the neo-antigenic third epitope of the first extra-cellular precipitate, the second moiety having an affinity for the third antigenic receptor on the second target cancer cells, the third bispecific reagent being administered prior to the administration of the first therapeutic agent and enabling the first extra-cellular precipitate to be retained for an extended period of time adjacent to the third antigenic receptor on the second target cancer cells.

44. A method according to 43 in which the first moiety of the third bispecific reagent has an affinity for the first antigenic epitope of the first extra-cellular precipitate.

45. A method according to 43 in which the first moiety of the third bispecific reagent has an affinity for the second antigenic epitope of the first extra-cellular precipitate.

46. A method according to 43 in which the first moiety of the third bispecific reagent has an affinity for the neo-antigenic third epitope of the first extra-cellular precipitate.

47. A method according to claim 1 and further comprising the step of administering to the living host a fourth bispecific reagent, the fourth bispecific reagent having two moieties, the first moiety having an affinity for one of the first antigenic epitope, the second antigenic epitope, and the neo-antigenic third epitope of the first extra-cellular precipitate, the second moiety having an affinity for the cancer-altered antigenic epitopes on the cancer-altered extra-cellular matrix, the fourth bispecific reagent being administered prior to the administration of the first therapeutic agent and enabling the first extra-cellular precipitate to be retained for an extended period of time adjacent to the cancer-altered antigenic epitopes on the cancer-altered extra-cellular matrix.

48. A method according to 47 in which the first moiety of the fourth bispecific reagent has an affinity for the first antigenic epitope of the first extra-cellular precipitate.

49. A method according to 47 in which the first moiety of the fourth bispecific reagent has an affinity for the second antigenic epitope of the first extra-cellular precipitate.

50. A method according to 47 in which the first moiety of the fourth bispecific reagent has an affinity for the neo-antigenic third epitope of the first extra-cellular precipitate.

51. A method according to claim 1 and further comprising the step of administering to the living host a fifth bispecific reagent, the fifth bispecific reagent having two moieties, the first moiety having an affinity for one of the first antigenic epitope, the second antigenic epitope, and the neo-antigenic third epitope of the first extra-cellular precipitate, the second moiety having an affinity for the antigenic epitopes on the relocated natural intra-cellular material, the fifth bispecific reagent being administered prior to the administration of the first therapeutic agent and enabling the first extra-cellular precipitate to be retained for an extended period of time adjacent to the antigenic epitopes on the relocated natural intra-cellular material.

52. A method according to 51 in which the first moiety of the fifth bispecific reagent has an affinity for the first antigenic epitope of the first extra-cellular precipitate.

53. A method according to 51 in which the first moiety of the fifth bispecific reagent has an affinity for the second antigenic epitope of the first extra-cellular precipitate.

54. A method according to 51 in which the first moiety of the fifth bispecific reagent has an affinity for the neo-antigenic third epitope of the first extra-cellular precipitate.

55. A method according to claim 31 and further comprising the step of administering to the living host a sixth bispecific reagent comprised of a molecule having a substantial affinity for the neo-antigenic epitope of the second extra-cellular precipitate, the sixth bispecific reagent further having a molecule with a substantial affinity for the third antigenic receptor on the second target cancer cells, the sixth bispecific reagent being administered prior to the step of additionally administering the second therapeutic agent and enabling the second extra-cellular precipitate to be retained for an extended period of time adjacent to the third antigenic receptor on the second target cancer cells.

56. A method according to claim 31 and further comprising the step of administering to the living host a seventh bispecific reagent comprised of a molecule having a substantial affinity for the neo-antigenic epitope on the second extra-cellular precipitate, the seventh bispecific reagent further having a molecule with a substantial affinity for the cancer-altered antigenic epitopes on the cancer-altered extra-cellular matrix, the seventh bispecific reagent being administered prior to the step of additionally administering the second therapeutic agent and enabling the second extra-cellular precipitate to be retained for an extended period of time adjacent to the cancer-altered antigenic epitopes on the cancer-altered extra-cellular matrix.

57. A method according to claim 31 and further comprising the step of administering to the living host a eighth bispecific reagent comprised of a molecule having a substantial affinity for the neo-antigenic epitope on the second extra-cellular precipitate, the eighth bispecific reagent further having a molecule with a substantial affinity for the antigenic epitopes on the natural intra-cellular material, the eighth bispecific reagent being administered prior to the step of administering the second therapeutic agent and enabling the second extra-cellular precipitate to be retained for an extended period of time adjacent to the antigenic epitopes on the natural intra-cellular material.

58. A method according to claim 40 and further comprising the step of administering to the living host an ninth bispecific reagent comprised of a molecule having a substantial affinity for the neo-antigenic epitope of the new form of the third therapeutic agent, the ninth bispecific reagent further having a molecule with a substantial affinity for the third antigenic receptor on the second target cancer cells, the ninth bispecific reagent to be administered prior to the step of administering the third therapeutic agent and enabling the new form of the third therapeutic agent to be retained for an extended period of time adjacent to the third antigenic receptor on the second target cancer cells.

59. A method according to claim 40 and further comprising the step of administering to the living host a tenth bispecific reagent comprised of a molecule having a substantial affinity for the neo-antigenic epitope on the new form of the third therapeutic agent, the tenth bispecific reagent further having a molecule with a substantial affinity for the cancer-altered antigenic epitopes on the cancer-altered extra-cellular matrix, the tenth bispecific reagent being administered prior to the step of administering the third therapeutic agent and enabling the new form of the third therapeutic agent to be retained for an extended period of time adjacent to the cancer-altered antigenic epitopes on the cancer-altered extra-cellular matrix.

60. A method according to claim 40 and further comprising the step of administering to the living host a eleventh bispecific reagent comprised of a molecule having a substantial affinity for the neo-antigenic epitope on the new form of the third therapeutic agent, the eleventh bispecific reagent further having a molecule with a substantial affinity for the antigenic epitopes on the natural intra-cellular material, the eleventh bispecific reagent being administered prior to the step of administering the third therapeutic agent and enabling the new form of the third therapeutic agent to be retained for an extended period of time adjacent to the antigenic epitopes on the natural intra-cellular material.

61. A method in accordance with claim 17 in which two indoxyl compounds are attached via a spacer molecule.

62. A method in accordance with claim 38 in which two indoxyl compounds are attached via a spacer molecule.

63. A method in accordance with claim 1 in which the first therapeutic agent is radio-labeled.

64. A method in accordance with claim 1 and further comprising the step of administering a cell killing process capable of selectively killing cancer cells that are super-sensitive including at least the third target cancer cells, the killing of the cells thereby causing the natural intra-cellular contents, including DNA, histone, and complexes of DNA-histone to be released into the extra-cellular fluid.

65. A method according to 64 in which the cell killing process includes the administering of at least a cytotoxic agent capable of selectively killing cells.

66. A method in accordance with claim 64 in which the administering of the cell killing process includes the administering of at least a non-cytotoxic agent capable of selectively killing cells.

67. A method in accordance with claim 1 in which the administering of cell killing process includes the administering of a procedure which alters the hormonal status and which is capable of selectively killing cells.

68. A method in accordance with claim 1 in which the administering of the cell killing process includes a cell killing process which is capable of inducing lysis.

69. A therapeutic agent being a radio-labeled soluble precipitable material for use as a pro-drug which is to be converted into an insoluble and non-digestible radio-labeled precipitate by the action of a non-mammalian enzyme when the therapeutic agent is administered to a living host containing a heterogeneous population of cancer cells including at least a sub-population of cancer cells being the target cells, each including a first antigenic receptor, the therapeutic agent being adjacent to the target cancer cells subsequent to the administration to the living host of a bispecific reagent, the bispecific reagent when administered to a living host being bound to the target cancer cells, the bispecific reagent containing two moieties, the first moiety which is a non-mammalian enzyme moiety being a first enzyme moiety, the bispecific reagent further containing a second moiety including a target agent moiety which has a substantial affinity for the first antigenic receptor of the target cancer cells, the therapeutic agent to be converted in the extra-cellular fluid of the living host, adjacent to the bispecific reagent, into an insoluble and non-digestible radio-labeled precipitate which is an extra-cellular radio-labeled precipitate by the action of the first enzyme moiety of the bispecific reagent, the bispecific reagent to be bound to the target cancer cells. the therapeutic agent being from a group consisting of peptides, including opio-melanins. of carbohydrates, including cellulose, chitosan, and chitin, of proteogylcans. of synthetic polymers. and of substituted indoxyl compounds containing molecular positions 1-7. the extra-cellular radio-labeled precipitate having an epitope selected from the group consisting of a first antigenic epitope, being an epitope which is an integral part

of the structure of the extra-cellular radio-labeled precipitate, a second antigenic epitope, and a neo-antigenic third epitope, the neo-antigenic third epitope not being present on the therapeutic agent, the extra-cellular radio-labeled precipitate remaining in the extra-cellular fluid adjacent to the bispecific reagent for an extended period of time sufficient to kill non-selectively all cells adjacent to the extra-cellular radio-labeled precipitate.

70. A therapeutic agent in accordance with claim 69 in which the therapeutic agent is cell impermeant.

71. A therapeutic agent in accordance with claim 69 in which a cell-impermeant chemical group is attached to the therapeutic agent, the cell-impermeant chemical group causing the therapeutic agent to be cell impermeant.

72. A therapeutic agent in accordance with claim 71 in which the cell-impermeant chemical group is selected from the group consisting of thiol chemical groups, anionic chemical groups, and cell impermeant chemical groups including peptides and polymers of a molecular weight greater than 1000 daltons.

73. A therapeutic agent in accordance with claim 69 which is inherently soluble.

74. A therapeutic agent in accordance with claim 69 in which the conversion of the therapeutic agent comprises the conversion of the therapeutic agent into a soluble intermediate molecule, the soluble intermediate molecule including the characteristic to be converted in the natural environment in the extra-cellular fluid into the extra-cellular precipitate.

75. A therapeutic agent in accordance with claim 74 in which the soluble intermediate molecule having the characteristic to be oxidized in the natural environment within the extra-cellular fluid, the oxidized soluble intermediate molecule being spontaneously dimerized, thereby forming the extra-cellular radio-labeled precipitate.

76. A therapeutic agent in accordance with claim 69 in which each of the indoxyl compounds is selected from the group consisting of indoxyl-lactam and indoxyl-glycosides, which when attached to position 3 of the indoxyl compounds are cleavable by the first enzyme moiety of the bispecific reagent, the material remaining after cleaving at position 3 being a soluble reactive intermediate molecule which can be oxidized and dimerized, thereby forming the extra-cellular radio-labeled precipitate.

77. A therapeutic agent in accordance with claim 69 in which each of the indoxyl compounds can be substituted to at least one of positions 4, 5, 6, and 7 of the indoxyl compound to reduce the ability of the extra-cellular radio-labeled precipitate to move in the extra-cellular fluid.

78. A therapeutic agent in accordance with claim 69 in which each of the indoxyl compounds includes phenyl compounds attached at position 4, 5, 6, or 7 of the indoxyl compound to reduce the ability of the extra-cellular radio-labeled precipitate to move in the extra-cellular fluid.

79. A therapeutic agent in accordance with claim 69 in which each of the indoxyl compounds includes benzyloxy compounds attached at position 5 of the indoxyl compounds to reduce the ability of the indoxyl compounds and the extracellular radio-labeled precipitate to move in the extra-cellular fluid.

80. A therapeutic agent in accordance with claim 69 in which each of the indoxyl compounds includes 5.5 –bi-indoxyls attached at position 5 of the indoxyls compounds to reduce the ability of the indoxyl compounds and the extracellular radio-labeled precipitate to move by at least one of diffusion and convective flow in the extracellular fluid.

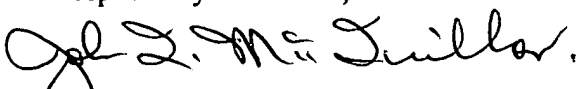
80. A therapeutic agent in accordance with Claim 69 in which each of the indoxyl compounds includes 5.5-bi-indoxyl compounds and the extracellular radio-labeled precipitate to move by at least one of diffusion and convective flow in the extracellular fluid.

81. A therapeutic agent in acordance with claim 80 in which two indoxyl compounds are attached via a spacer molecule.

82. A therapeutic agent in accordance with claim 69 which has a soluble moiety and an insoluble moiety, the soluble moiety providing a solubilizing effect on the insoluble moiety and being cleaved by the enzyme moiety of the bispecific reagent from the insoluble moiety, the solubilizing effect of the soluble moiety being thereby reduced and the remaining material being available to form the extra-cellular precipitate.

83. (amended) A therapeutic agent in accordance with claim 69 which is radio-labeled.

Respectfully submitted,



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October 30, 2003